REMARKS

In the Office Action dated September 5, 2003, claims 1, 5, 8-9 and 11-12 are pending and under consideration. Claim 12 is rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to satisfy the written description requirement. Claim 12 is also rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. Claims 1 and 5 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to meet the written description requirement. Claims 1 and 5 are further rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. In addition, claims 1, 5 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. The Examiner has also objected to the application for certain alleged informalities.

This Response addresses each of the Examiner's rejections. Applicant therefore respectfully submits that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

The Examiner has objected to the word "novel" in the title of the application. Applicant has amended the title to recite "nucleic acid encoding α chain of human IL-11 receptor", as the Examiner has suggested.

The Examiner has also pointed out that the sequences at page 21, Table 2 of the instant specification must be accompanied with sequence identifiers. Applicant has amended Table 2 to insert the sequence identifiers.

Claim 12, drawn to an isolated nucleic acid molecule encoding a mammalian IL-11 receptor α-chain, is rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to satisfy the written description requirement.

The Examiner contends that claim 12 encompasses mammalian nucleic acid homologs encoding IL-11 receptor α-chains having undisclosed amino acid sequences. The Examiner is of the opinion that, with the exception of human amino acid sequence as set forth in SEQ ID NO: 5, none of the mammalian IL-11 receptor α-chains meet the written description requirement of 35 U.S.C. 112, first paragraph. According to the Examiner, one skilled in the art cannot envision the detailed chemical structure of the encompassed amino acid sequences, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity of simplicity of the method of isolation.

Applicant respectfully submits that according to the Guidelines provided by the United States Patent & Trademark Office, the written description can be satisfied by establishing possession of the invention by way of actual reduction to practice, or by way of describing the invention with sufficiently detailed, relevant identifying characteristics, i.e., complete or partial structure, physical and/or chemical properties, correlation between structure and function, or some combination thereof. 66 Federal Register 1099-1111 (2001), at 1106.

In this regard, the present specification describes the isolation of a nucleic acid encoding murine IL-11 receptor alpha chain, and the isolation of a nucleic acid encoding human IL-11 receptor alpha chain by using murine sequence-derived probes under conditions consistent with those recited in claim 12. The present specification also describes the structural characteristics of mammalian IL-11 receptor alpha chains, particularly by providing examples of the common structural features shared by a murine IL-11 receptor alpha chain and a human IL-11 receptor alpha chain, including the Ig domain, the haemopoietin domain, the conserved cysteins and the WSXWS motif. See, e.g., pages 25-26 of the specification. Furthermore, the specification clearly describes the functional features of mammalian IL-11 receptor alpha chains

including, e.g., an IL-11 receptor α-chain binds IL-11 and may interact with gp130 protein to mediate an IL-11 induced proliferative or differentiative response. See pages 27-30 of the specification. Therefore, Applicant respectfully submits that the nucleic acid molecule of claim 12, drawn to an isolated nucleic acid molecule encoding a mammalian IL-11 receptor α-chain, is adequately described in the specification in a manner consistent with the written description requirement.

Applicant has also added claim 31 to further delineate the functional feature of the mammalian IL-11 receptor α-chain by reciting "wherein said mammalian IL-11 receptor α-chain interacts with gp130 protein to mediate an IL-11 induced proliferative or differentiative response." As submitted above, such functional delineation is supported by the specification, e.g., pages 27-30. Claim 32 is added to further delineate the structural feature of the mammalian IL-11 receptor α-chain by reciting "wherein said mammalian IL-11 receptor α-chain comprises Trp-Ser-Xaa-Trp-Ser (SEQ ID NO:1)", as described in the specification at page 2, line 20, for example. Applicant respectfully submits that the nucleic acid molecules of claims 31-32 are adequately described structurally and functionally in the specification, consistent with the written description requirement.

In view of the foregoing, it is respectfully submitted that the rejection of claim 12 under the written description requirement of 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is therefore respectfully requested.

Claims 1 and 5, drawn to isolated nucleic acid molecules encoding a human IL-11 receptor α-chain, are also rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to meet the written description requirement.

The Examiner states that, with the exception of SEQ ID NO: 4 and degenerate equivalents thereof, one skilled in the art cannot envision the detailed chemical structure of the encompassed nucleic acids, and therefore, conception is not achieved until reduction to practice has occurred. In addition, the Examiner contends that the claims encompass nucleic acid molecules which are only portions of the full-length sequence of SEQ ID NO:4, as well as variants having one or more nucleotide deletions, insertions and/or additions made to SEQ ID NO:4. The Examiner argues that the specification and the claims do not set forth the distinguishing attributes shared by the genus of the claimed molecules, or the portion of the molecules that is responsible for functional activity.

Applicant respectfully submits that the present specification adequately describes the claimed nucleic acid encoding human IL-11 receptor alpha chain. In the first instance, the present specification discloses the isolation of a nucleic acid encoding a human IL-11 receptor alpha chain, as set forth in SEQ ID NO: 4. By way of examples, the present specification also describes the structural characteristics of the human IL-11 receptor alpha chain encoded by the nucleic acid molecule as set forth in SEQ ID NO: 4, including the Ig domain, the haemopoietin domain, the conserved cysteins and the WSXWS motif. See, e.g., pages 25-26 of the specification. Furthermore, the specification also describes the functional features of the human IL-11 receptor alpha chain encoded by the nucleic acid molecule as set forth in SEQ ID NO: 4, including, e.g., its ability to bind IL-11 and interact with gp130 protein to mediate an IL-11 induced proliferative or differentiative response. See pages 27-30 of the specification. Therefore, Applicant respectfully submits that the nucleic acid molecules of claims 1 and 5, drawn to an isolated nucleic acid molecule encoding a human IL-11 receptor α-chain, is

adequately described in the specification in a manner consistent with the written description requirement.

Applicant has also added claim 33 to further delineate the functional feature of the human IL-11 receptor α-chain by reciting "wherein said human IL-11 receptor α-chain interacts with gp130 protein to mediate an IL-11 induced proliferative or differentiative response." Claim 34 is added to further delineate the structural feature of the human IL-11 receptor α-chain by reciting "wherein said human IL-11 receptor α-chain comprises Trp-Ser-Xaa-Trp-Ser (SEQ ID NO:1)". Applicant respectfully submits that the nucleic acid molecules of claims 33-34 are adequately described both structurally and functionally in the specification, consistent with the written description requirement.

In view of the foregoing, it is respectfully submitted that the rejection of claims 1 and 5 under the written description requirement of 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is therefore respectfully requested.

Claim 12 is further rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. Claims 1 and 5 are also rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

The Examiner states that the specification, while enabling for an isolated nucleic acid molecule which encodes an α chain of a human IL-11 receptor polypeptide as set forth in SEQ ID NO: 5, does not reasonably provide enablement for a nucleic acid molecule encoding a mammalian IL-11 receptor α-chain, as recited in claim 12, or a nucleic acid molecule encoding a human IL-11 receptor α-chain, as recited in claims 1 or 5. The Examiner contends that it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

In response, the Examiner's attention is respectfully directed to the Declaration by Dr. Hilton (Hilton Declaration), submitted with the §1.116 Response dated April 9, 2003. A copy of the Declaration is provided again herewith for the Examiner's easy reference.

In the Declaration, Dr. Hilton testifies that IL-11Rα has been cloned from various sources including from mouse and human cells. Dr. Hilton testifies that, to clone a nucleic acid molecule comprising a nucleotide sequence encoding IL-11Rα from murine cells, a series of oligonucleotides were generated encompassing the nucleotide sequence encoding the signature motif, Trp-Ser-Xaa-Trp-Ser ("WSXWS"). The oligonucleotides were used to screen a commercially available adult mouse liver cDNA library. *See* Examples 1-2 and Table 2 in the specification. As testified by Dr. Hilton, a clone, Nr_1-AZ-36, which contained a nucleotide sequence encoding an amino acid sequence having the motif characteristic of the haemopoietin receptor family, was then identified from the cDNA library. From the sequence of Nr_1-AZ-36, two new primers were designed and were used to rescreen the cDNA library. The murine IL-11Rα cDNA was thus cloned and expressed in a cell system. The binding studies of the murine IL-11Rα were conducted. *See* Examples 8-13 in the specification. *See* Hilton Declaration ¶ 3-5.

Dr. Hilton also testifies that, using the two new primers obtained above, full-length murine IL-11Rα cDNA was cloned. *See* Example 10 in the specification. The full-length cDNA sequences contained an open reading frame of 1296 bp which encoded a protein of 432 amino acids in length. The predicted primary sequence included a potential hydrophobic leader sequence (residues 1-23), extracellular domain with two potential N-linked glycosylation sites (residues 24-367), transmembrane domain (residues 368-393) and short cytoplasmic tail (residues 394-432). The extracellular domain contained residues characteristic of a classical haemopoietin domain (*see* Figures 1 and 2 in the specification), including proline residues

preceding each 100 amino acid sub-domain, four conserved cysteine residues, a series of polar and hydrophobic residues and a WSXWS motif. The overall structure and primary sequence of the new receptor (IL-11Rα) were most similar to the IL-6 receptor α-chain (24% amino acid identity), the CNTF receptor α-chain (22% amino acid identity) and the p40 subunit of IL-12 (16% amino acid identity). Therefore, Dr. Hilton testifies that the approach employed was very successful in identifying the IL-11Rα clone. *See* Hilton Declaration ¶ 6.

Dr. Hilton further testifies that the human form of IL-11Rα was then cloned, also employing hybridization of murine IL-11Rα cDNA. *See* Example 14 in the specification. Dr. Hilton testifies that the detection and cloning of variants of murine or human IL-11Rα genetic molecules is accomplished using similar techniques as discussed above and as described in the specification. For example, by employing the approach above, the inventor yielded a number of variants, designated Nr1-30.2, Nr1-30.3, Nr1-30.4 and Nr1-30.17. *See* Figure 1A and Example 12. *See* Hilton Declaration ¶ 7-8.

Accordingly, Dr. Hilton testifies that the specification, particularly Example 10, enables one skilled in the art to make and use the hybridization variants that retain the features of the IL-11 R α-chain. Specifically, Dr. Hilton declares that using cDNA or probes from murine or human IL-11Rα cDNA, homologous cDNA molecules would be detected from different cells or from the same cells from different sources. Dr. Hilton further testifies that any hybridization variants would still retain either some or all of the features of the IL-11Rα such as a hydrophobic leader sequence, extracellular domain with potential N-linked glycosylation sites, transmembrane domains and a short cytoplasmic tail. Dr. Hilton testifies that the extracellular domain would still contain residues characteristic of a classical haemopoietin domain including proline residues, conserved cysteine residues and a WSXWS motif. *See* Hilton Declaration ¶ 9. Finally, Dr.

Hilton declares that hybridization variants would be readily identifiable which would hybridize to SEQ ID NO:4 or its complementary form under high stringency hybridization conditions. *See* Hilton Declaration ¶ 10.

In this connection, Applicant observes that subsequent to the filing of the §1.116 Amendment and Dr. Hilton's Declaration responsive to the Final Action, the Examiner issued an Advisory Action on April 24, 2003. In the Advisory Action, the Examiner reasserted the written description rejection only, without commenting on the enablement rejection.

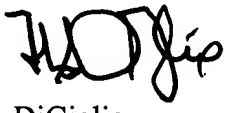
Applicant respectfully submits that the Declaration supports the understanding that it would not take undue experimentation for those skilled in the art to obtain the nucleic acid molecule as presently claimed in claims 1, 5 and 12. Therefore, the rejection of claims 1, 5 and 12 as failing to meet the enablement requirement of 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is therefore respectfully requested.

Claims 1 and 5 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. The Examiner contends that it is unclear how the claimed nucleic acid molecule encoding an α-chain of human IL-11 receptor could hybridize to both SEQ ID NO:4 and the complement of SEQ ID NO:4.

Applicant has amended independent claim 1 to recite "wherein said nucleic acid molecule comprises the nucleotide sequence as set forth in SEQ ID NO:4 or a nucleotide sequence which hybridizes to the complementary form of SEQ ID NO: 4." Applicant submits that claim 1 as amended is not indefinite. Withdrawal of the rejection of claims 1 and 5 under 35 U.S.C. §112, second paragraph, is therefore respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Douglas J. Hilton	**Examiner:**	Sarada C Prasad
Serial No.:	09/532,263	**Art Unit:**	1646
Filed:	March 22, 2000	**Docket:**	10296A

For: A NOVEL HAEMOPOIETIN RECEPTOR

Assistant Commissioner for Patents
United States Patent and Trademark Office
Washington, D.C., 20231

DECLARATION PURSUANT TO 37 CFR §1.132

I, Douglas James Hilton, hereby declare as follows:-

1. I am an Applicant and co-inventor of subject matter (hereinafter referred to as the "Invention") disclosed and claimed in U.S. Patent Application No. 09/532,263 (hereinafter referred to as the "Application") which is currently under examination before the U.S. Patent and Trademark Office.

2. I hold a Bachelor of Science (BS) Degree in Biochemistry and a Doctorate Degree in Molecular Hematology. I have conducted research in the field of molecular hematology since 1986 and have authored numerous publications in this field. A true and correct copy of my Curriculum Vitae is attached hereto as **Exhibit 1**.

3. The Invention relates generally to a novel haemopoitin receptor and a method for cloning genetic sequences encoding same. More particularly, the Invention relates to the Interleukin-11 (IL-11) receptor α chain (IL-11Rα) which has been cloned from various sources including from mouse and human cells.

4. IL-11 is a functionally pleiotrophic molecule which was initially characterized by its ability to stimulate proliferation of the Inteleukin-6 (IL-6)-dependent plasmacytoma

cell line, T1165. It has since been determined to be involved in multi-potential haemopoietin progenitor cell proliferation, enhancement of megakaryocyte and platelet formation, stimulation of acute phase protein synthesis and inhibition of adipocyte lipoprotein lipase activity. It is a physiologically important molecule, therefore, and the ability to modulate its activity will have significant medical benefits in terms of therapy and the development of diagnostics. One convenient way of modulating IL-11 function is through its receptor, IL-11Rα.

5. Haemopoietin receptors generally comprise two chains, the α-chain and the β-chain. To clone a nucleic acid molecule comprising a nucleotide sequence encoding IL-11Rα from murine cells, a series of oligonucleotides were generated encompassing the nucleotide sequence encoding the signature motif, Trp-Ser-Xaa-Trp-Ser (WSXWS using single amino acid letter code), wherein Xaa (X) is any amino acid. These were used to screen a commercially available adult mouse liver cDNA library. This is described in detail in Examples 1 and 2 using oligonucleotides as described in Table 2.

A clone was identified, designated Nr_1-AZ-36 which contained a nucleotide sequence encoding an amino acid sequence having the motif characteristic of the haemopoietin receptor family. From this sequence, two more oligonucleotide primers were designed; see oligonucleotides #26 and #60, Table 2. These were used to re-screen the cDNA library. The murine IL-11Rα cDNA was thus cloned, expressed in a cell system and binding studies conducted as described in Examples 8-13.

6. For cloning of the full length murine IL-11Rα cDNA, reference should be made to Example 10. In this Example, a second murine liver cDNA library was screened using oligonucleotides #26 and #60 which are directed to the 5' end of the original Nr_1-AZ-36 clone. The key to characterizing the murine IL-11Rα cDNA was to determine its putative amino acid sequence after translation. Analyses of the cDNA sequences revealed an open reading frame of 1296 bp which encoded a protein of 432 amino acids in length. The

predicted primary sequence included a potential hydrophobic leader sequence (residues 1-23), extracellular domain with two potential N-linked glycosylation sites (residues 24-367), transmembrane domain (residues 368-393) and short cytoplasmic tail (residues 394-432). The core molecular weight of the mature receptor has been initially estimated to be approximately 36,000 daltons.

The extracellular domain contained residues characteristic of a classical haemopoietin domain (Figures 1 and 2 in the Application), including proline residues preceding each 100 amino acid sub-domain, four conserved cysteine residues, a series of polar and hydrophobic residues and a WSXWS (see paragraph 5 above) motif. The haemopoietin receptor domain of the new receptor was preceded by an 87 amino acid immunoglobulin-like domain and followed by 37 amino acids before the transmembrane domain. Regarding its overall structure and its primary sequence (see Figure 2 of the Application), the new receptor was most similar to the IL-6 receptor α-chain (24% amino acid identity), the CNTF receptor α-chain (22% amino acid identity) and the p40 subunit of IL-12 (16% amino acid identity). This approach, therefore, of considering the putative translational data was very successful in identifying the IL-11Rα clone.

7. The human form of IL-11Rα was then cloned as described in Example 14, again using hybridization of murine IL-11Rα cDNA.

8. The detection and cloning of variants of murine or human IL-11Rα genetic molecules would be accomplished using similar techniques as discussed above and as provided in the Application. In fact, the approach adopted yielded a number of variants, possibly splice variants, designated Nr1-30.2, Nr1-30.3, Nr1-30.4 and Nr1-30.17 (see Figure 1A and Example 12 in the Application).

9. My patent advisors have shown me a copy of the Official Action from the U.S. Patent and Trademark Office which *inter alia* alleges that the skilled artisan would not be

able to utilize the information in Example 10 to generate hybridization variants with the characteristics of IL-11Rα.

With respect, I totally disagree with this allegation. Using cDNA or probes from murine or human IL-11Rα cDNA, homologous cDNA molecules would be detected from different cells or from the same cells from different sources. Any hybridization variants would still retain either some or all of the features of the IL-11Rα such as a hydophobic leader sequence, extracellular domain with potential N-linked glycosylation sites, transmembrane domains and a short cytoplasmic tail.

The extracellular domain would still contain residues characteristic of a classical haemopoietin domain including proline residues, conserved cysteine residues and a WSXWS motif.

10. It is my considered opinion that hybridization variants would be readily identified which would hybridize to SEQ ID NO:4 or its complementary form under high stringency hybridization conditions. This would be readily characterized using the methods described in the Application.

11. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 3th April 2003 _____

Douglas James Hilton